

A Pivotal Multi-Center, Randomized, Controlled, Single-Blinded Study Comparing the Silver Nitrate Coated Indwelling Pleural Catheter (SNCIPC) to the Uncoated PleurX® Pleural Catheter for the Management of Symptomatic, Recurrent, Malignant Pleural Effusions

Statistical Analysis Plan

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Definitions of Terms

AE(s)	Adverse event(s)
ADE(s)	Adverse device effect(s)
ATC	Anatomical Therapeutic Chemical
C	Celsius degree
CBC	Complete blood count
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CP	Conditional power
CRO	Contract research organization
CRP	C-reactive protein
CT	Computed tomography
CXR	Chest X-Ray
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EOS	End of study
F	Fahrenheit degree
FDA	Food and Drug Administration
HR	Hazard Ratio
ICF	Informed Consent Form
ICP-MS	Inductively coupled plasma mass spectrometry
IEC	Institutional Ethics Committee
IFU	Instructions for Use
IPC	Indwelling pleural catheter
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-treat
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver function tests
LSLV	Last subject last visit
m	Meter
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/d	Milligrams per day
min	Minimum
mL	Milliliter

mm	Millimeter
MPE	Malignant pleural effusion
MRU	Medical resource utilization
N	Number of subjects
NI	Non-inferiority
OTC	Over-the-counter
PIS	Patient information sheet
PP	Per protocol
QoL	Quality of Life
SADE	Serious adverse device effect
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Statistical analysis software
SD	Standard deviation
SNCIPC	Silver Nitrate-Coated Indwelling Pleural Catheter
SOP	Standard operating procedure
TEAE(s)	Treatment-emergent adverse event(s)
UADE(s)	Unanticipated adverse device effect(s)
UK	United Kingdom
US	United States
USADE(s)	Unanticipated serious adverse device effect(s)
VAS	Visual Analog Scale
WHO	World Health Organization

2. INTRODUCTION

Pleural effusions, or excess fluid build-up between the pleural linings of the lung, affect over 1 million people in the United States annually.¹ While some effusions are asymptomatic, most result in significant breathlessness for patients. Of these, over 150,000 effusions are secondary to a malignancy,^{1,2} and most of those are recurrent and unresponsive to traditional medical management. The prognosis for patients with malignant pleural effusion (MPE) is nearly always poor, with average life expectancy following diagnosis of 4-6 months.¹

Treatment for MPE has traditionally focused on 3 approaches: repeat thoracentesis, chemical pleurodesis, or placement of an indwelling pleural catheter (IPC). Although a single thoracentesis procedure is the least invasive and least expensive option, relief is usually short lived. Repeated thoracentesis is possible but requires the patient to visit the clinic frequently in order to manage their symptoms. This approach does not lead to consistent symptom control, risks infection, and is particularly time consuming for subjects with a short life expectancy.

The most commonly used alternative, chemical pleurodesis, is intended to fully resolve the effusions but requires a typical inpatient hospital stay of 4 to 9 days^{2,3} and may result in significant pain and fever following the introduction of the pleurodesis agent. The agent is usually introduced via a chest tube (inserted under local anesthetic) or insufflated during thoracoscopy (which may be performed under sedation or general anesthetic). The most commonly used agent for pleurodesis worldwide is talc.^{1,2,4} Although talc is effective, it still fails to achieve pleurodesis in a significant proportion of subjects. Additionally, even for those talc subjects that initially achieve pleurodesis, up to 30% have recurrence after 30 days.^{1,4} Silver nitrate has also been used and studied extensively for pleurodesis, both in animals and in humans.⁶⁻²⁵ From 1932 to 1983, silver nitrate was one of the primary agents to initiate pleurodesis for pneumothorax and other conditions, including pleural effusions.^{10,12-16} More recently, a clinical study in 2005 showed silver nitrate to be effective in achieving pleurodesis with minimal side effects.⁹ In 2007, a clinical study of over 600 subjects showed silver nitrate to be effective in achieving pleurodesis.⁸

By contrast, an IPC is typically placed on an outpatient basis using local anaesthesia, and can be used to drain a recurrent pleural effusion at home by the subject or caregiver using vacuum bottles. The market-leading IPC is the PleurX Pleural Catheter, manufactured by CareFusion, Inc. It is currently indicated for 1) the palliation of dyspnea due to pleural effusion and 2) for providing pleurodesis.

The ideal approach to managing MPE, therefore would be to reliably and permanently resolve effusions (i.e., achieve pleurodesis), in a short period of time and in an outpatient setting, with lower levels of pain and lower costs. This is particularly true if the outpatient management of MPE can provide equivalent or even favorable quality of life (QoL) results compared to other

(inpatient) treatment options without negatively impacting mortality.²⁶ In addition to the cost-savings, outpatient treatment, when possible, is important because patients with MPE are older, on average (between 60 to 67 years old)^{5, 26-28} with a relatively short life expectancy. Although the PleurX catheter is currently indicated for pleurodesis, its rate of achieving pleurodesis is typically lower than that of talc (46% in a median of 26.5 days and mean of 56 days⁵ for PleurX vs 78% talc insufflation pleurodesis success at 30 days).⁴ Furthermore, the average time required to achieve pleurodesis using PleurX (around 2 months)⁵ is less than optimal for clinicians and patients who desire both a timely and definitive resolution of the pleural effusion symptoms. The SNCIPC has been designed with the aim of enhancing the PleurX pleural catheter's pleurodesis performance by the addition of an established pleurodesis agent, silver nitrate. A secondary benefit to this approach for the relatively small proportion of patients who potentially may not achieve pleurodesis even with the addition of silver nitrate is the ability for those patients to still drain the pleural effusions through the same catheter, without the need for an additional invasive procedure.

3. STUDY OBJECTIVES

The primary objective of this prospective, multicenter, randomized, controlled, single-blinded pivotal study is to demonstrate that the Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) shows superiority compared to the PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence by 30 days. This will be achieved by evaluating the proportion (%) of patients achieving pleurodesis without recurrence by 30 days after catheter placement, where pleurodesis is defined as:

- The collection of a minimum of 3 consecutive drainages of ≤ 50 mL of pleural fluid over a minimum of 5 days (which begin with the first drainage of ≤ 50 mL)
- and
- Chest X-Ray (CXR), which shows opacification due to pleural fluid occupying less than one quarter of the hemithorax (as judged by the investigative study center and the blinded third party central radiology service)

The date of pleurodesis is defined as the day on which the first of 3 consecutive drainages of ≤ 50 mL was recorded. Recurrence is defined as symptomatic pleural effusion confirmed by CXR and CT scan with an estimated >300 mL of fluid in the treated hemithorax.

The secondary objectives of this study are to summarize measures of time to confirmed pleurodesis and time to recurrence.

For each of the secondary objectives; when non-inferiority is achieved, superiority will subsequently be tested to show SNCIPC superiority over the PleurX Catheter.

The following exploratory objectives will be evaluated including device safety, device performance, quality of life (QoL) and medical resource utilization (MRU).

4. STUDY DESIGN

4.1 General Design

This is a prospective, multicenter, randomized, controlled, single-blinded pivotal study of the SNCIPC as compared to the PleurX Pleural Catheter when used as intended to palliate dyspnea in subjects with recurrent pleural effusions. The study is designed to provide powered evidence that the SNCIPC shows superiority compared to PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence at 30 days.

Eligible subjects will have undergone at least 1 successful lung expansion after thoracentesis and are experiencing a reoccurrence of pleural effusions that are causing dyspnea. Subjects or their caregivers (friend, family member, or paid healthcare professional) must be able to perform at-home pleural effusion drainage for up to 90 days post-IPC insertion. Clinicians, caregivers, and patients will be adequately trained to ensure that the drainage procedure and measurement of drainage volumes will be consistent. Subjects will be recruited during consult for their procedure and will return to the study center to be randomized to receive either the SNCIPC (treatment group) or the PleurX Pleural Catheter (control group) in a 2:1 randomization ratio on the day of the procedure. Subjects will be considered enrolled at the time of randomization. A trained study staff member will insert the IPC in a dedicated procedure room or operating suite using the same technique as for insertion of the PleurX catheter. At the time of insertion, the pleural cavity should be maximally drained (as limited by subject signs or symptoms). The day of IPC insertion is defined as Day 0. Subjects should have a post-insertion CXR (posterior-anterior and lateral) within 6 hours of the conclusion of the procedure, but after they have been maximally drained. Assessments for trapped lung should be done at Day 14 and Day 30 post insertion.

After IPC insertion, subjects will be evaluated at 14-day (± 2), 30-day (± 2), 60-day (± 3), and 90-day (± 3) follow-up visits plus a telephone assessment by study center personnel at 7 (± 2) days, 45 (± 3) days, and 75 (± 3) days.

In addition, subjects must call the study center to make an appointment for an unscheduled visit to assess for pleurodesis and potential IPC removal once they measure an output of ≤ 50 mL of pleural fluid on 3 consecutive drainages over a minimum of 5 days. Once pleurodesis is confirmed every effort should be made to schedule IPC removal as soon as feasible. At the time of SNCIPC removal, the SNCIPC should be shipped to the designated central analytical laboratory for residual silver testing.

Safety and efficacy assessments will be performed as noted in the Schedule of Procedures and Assessments.

Chest X-Rays will be performed by the site as indicated in the Schedule of Procedures and Assessments. Centrally read Chest X-Rays will be analyzed at 4 planned timepoints which are pre-catheter placement (baseline), post-catheter placement, 30-day, and any reoccurrence.

End of study (EOS) is defined as the date the last subject completes the last visit of the study (LSLV).

Face-to-face follow-up visit assessments to include, as appropriate:

- Maximal catheter drainage (fluid sample retained for subjects who received SNCIPC) and CXR
- Determination of pleurodesis
- Determination of previously unidentified trapped lung (Day 14 and Day 30)
- Record of adverse event(s) [AE(s)] since last visit
- Record of further pleural interventions needed
- Assessment of recurrence post-pleurodesis
- Record of current oncological treatment
- Review of subject diary (temperature, drainage volumes, over-the-counter [OTC] and prescription medications, oxygen use, chest pain and dyspnea scores, and unplanned hospital or emergency department visits)
- Assessment of analgesia requirements
- Examination of drain insertion site (with removal of stitches if necessary)
- Physical examination (including vital signs, oxygen saturations, and respiratory rate)
- Collection of blood samples (for subjects with SNCIPC, this includes samples for serum silver analysis)
- Serum and/or urine pregnancy test
- Record of MRU

Telephone assessments to include, as appropriate:

- Record of adverse events since last visit
- Record of further pleural interventions needed
- Record of current oncological treatment
- Record of MRU
- Assessment of analgesia requirements
- Review of subject diary (temperature, drainage volumes, OTC and prescription medications, oxygen use, chest pain and dyspnea scores and unplanned hospital or emergency department visits)
- Assessment of pleurodesis
- EQ-5D-5L health status questionnaire

If the pleurodesis criteria are met, subjects will be scheduled for catheter removal.

If the pleurodesis criteria are not met at the end of their trial follow-up period, or at the end of the study period, the catheter may be left in place to provide palliation of symptoms at the Investigator's discretion. If clinically appropriate in the opinion of the Principal Investigator, patients will be offered the choice of having their catheter removed or, if regular drainage with symptomatic benefit continues, having the catheter left in place. Subjects who choose to have their catheter removed will be made aware that they may require insertion of a standard PleurX catheter, or an alternative procedure (or procedures) for the purposes of pleural fluid management. Patients who choose to have their catheter remain in place will revert to standard clinical follow-up.

The primary efficacy endpoint of pleurodesis will be measured at 30 days and the findings will be verified via masked core lab review of the chest x-ray. Subjects will be enrolled in the study through 90 days.

4.2 Discussion of Study Design

The advantage of the single-blind study is that subjects will not be aware of the treatment received which will lead to reduction of operational bias and bias in study measurements. Using an active control as the control group contributes to the validity of the treatment effect in order to make label claims. A disadvantage of using the active control is that the comparison of treatment to the active control may be biased if the effect of the active control is greater than expected. The multicenter design of the study is advantageous in that treatment effects can be generalized across sites, as long as the treatment effects across sites are comparable.

4.3 Method of Assignment of Subjects to Treatment Groups

Subjects will be randomly allocated to treatment groups on the day of IPC placement. The randomization will be stratified in a 2:1 ratio of treatment group and control group, respectively. The randomization codes will be generated within the Biometrics Department of Chiltern International Inc. by a statistician not involved in the study.

In order to ensure that the study treatment groups are balanced, randomization numbers will be assigned to the two study treatments in blocks, with the 2:1 randomization ratio preserved within each block. Subject randomization will be performed according to a computer-generated randomization schedule prepared by the Sponsor's (or designee) statistician and programmed into an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) to assure subjects are centrally randomized. Site staff will connect to the IVRS/IWRS to enter the subject's information after confirming eligibility. The IVRS/IWRS will provide site staff with a randomization code linked to the study device

to be used. The Investigators will randomize the subjects in ascending order of the site-specific randomization lists.

4.4 Blinding

Study subjects will be blinded since the external components for either study device are the same; however, the Principal Investigators will remain unblinded since the 2 study devices can be readily distinguished by outward appearance prior to placement. The independent radiologist(s) who will evaluate the scans will be blinded to the identity of the investigational product given to the subject.

The blind will be broken at the end of the study, after every subject has completed the study, been entered in the database, and the database is locked.

The Data Safety Monitoring Board (DSMB) or other regulatory bodies (i.e., FDA, IRB/IEC) will have access to the unblinded data when necessary for reviewing, evaluating and/or reporting on subject safety issues or concerns during the conduct of the clinical research trial.

There will be 2 separate biometrics teams, a blinded team and an unblinded team, working on this study. This is a single-blinded study; a dummy randomization scheme will be followed when programming summary outputs so as not to program with bias on safety and efficacy outputs prepared for the DSMB. However, actual treatment codes will be used to validate programs for production of the displays. This process will be as follows:

- The Biometrics unblinded statistician will request treatment assignment from the randomization vendor. These will be sent as an electronic file(s) in a secure manner to the unblinded statistician in the appropriate timeframe prior to each DSMB meeting. The unblinded statistician will use these to perform a reconciliation of the treatment assignments in the clinical database.
- The unblinded statistician will give the unblinded randomization codes to the DSMB statistical programmer who will copy the file(s) onto the data server in a restricted area providing access only to the unblinded team.
- The unblinded project team will then create a dummy randomization scheme for the blinded project team to use.
- The blinded project team from Biometrics department will program the defined tables, listings, and figures for the study using the dummy randomized data.
- The unblinded team will run these programs using the unblinded data to provide outputs for the DSMB.

The randomization codes and the complete generation procedure will be filed in a secure location by Chiltern International Inc. until the study database is opened. A copy of the list will be sent to CareFusion 2200, Inc for the purpose of assigning the kits to the subjects.

4.5 Determination of Sample Size

The sample size was calculated based on the primary efficacy endpoint: rate of pleurodesis without recurrence at 30 days. A sample size of 79 subjects in the study device group and 40 subjects in the control study device group is planned for the study based on 80% power to demonstrate superiority of the study device group over the control group with a one-sided type I error 2.5%.

The unadjusted rates of pleurodesis are assumed to be 75% for the study device group, and 35% for the control device. Assuming 20% subjects will have trapped lung who cannot achieve pleurodesis, and 20% of the remaining subjects will drop out before reaching the 30 days follow-up, and will be considered as failures for the primary endpoint, the adjusted pleurodesis rates are 48% for the study device group and 22% for the control device.

The sample size for superiority was computed with the following assumptions:

- One-sided test
- Type I error rate: 2.5%
- 80% power to demonstrate superiority of the study device group over the control group
- Rate of pleurodesis at 30 days with consideration for trapped lung and dropout, Control: 22%
- Rate of pleurodesis at 30 days with consideration for trapped lung and dropout, Test: 48%
- Expected Randomization Ratio of T:C is 2:1

Subjects who are discontinued/withdrawn after entering the randomized treatment phase will not be replaced.

When 80 subjects reach the primary endpoint, an unblinded sample size reassessment based on promising zone approach will be performed as detailed in Section 6

5. BASELINE, EFFICACY and SAFETY EVALUATIONS

5.1 Schedule of Evaluations

Study Visit Procedure	Pre-Screening ^a	Screening (Day -14 to Day -1)	Baseline Assessment ^b (Day -3 to Day 0)	Insertion (Day 0)	Follow-Up Visits Study Day (+/- Days)						Follow-Up to Confirm Pleurodesis ^d	Pleural Catheter Removal	Confirm Recurrence ^e	Between Follow-Up Visits
					7 ^c (+/-2)	14 (+/-2)	30 (+/-2)	45 ^c (+/-3)	60 (+/-3)	75 ^c (+/-3)	90 (+/-3)			
I/E criteria and PIS	X	X	X											
Sign consent form(s)		X												
Medical history			X											
Prior and concomitant medications ^f			X		X	X	X	X	X	X	X			
Physical examination ^g			X	X		X	X		X		X			
Assessment of analgesia requirements					X	X	X	X	X	X	X			
Serum (S) or urine (U) pregnancy test ^h		S (X)	(U)								S			
Silver nitrate hypersensitivity test ⁱ		(X)												
Chest X-ray ^j		(X)	X	X		X	X		X		X	X	X	
CT Scan													X	
Randomization (within 24 hours prior to IPC insertion)				X										
Collect blood samples for clinical safety tests ^k		X	X			X	X		X		X			
Collect blood samples for serum silver testing (SNCIPC only) ^l				X		X	X		X		X	X		
Maximal pleural drainage ^m				X		X	X		X		X			X
Pleural fluid samples for silver testing (SNCIPC only) ⁿ				X		X	X		X		X			
Medical resource utilization ^o				X	X	X	X	X	X	X	X	X		X
Diary completion ^p					X	X	X	X	X	X	X	X		X
QoL measurements (pain and dyspnea) ^{p,q}			X	X	X	X	X	X	X	X	X			X
QoL measurements (EQ-5D-5L health status questionnaire) ^q			X	X	X	X	X	X	X	X	X			
AE monitoring			X	X	X	X	X	X	X	X	X	X		X
Previously unidentified trapped lung ^r						X	X							
Residual silver testing (SNCIPC only) ^s												X		

Statistical Analysis Plan

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Abbreviations: CBC = complete blood count; eCRF = electronic case report form; CRP = C-reactive protein; CXR = chest X-ray; EQ-5D-5L = European Quality of Life-5 Dimensions; I/E = inclusion/exclusion; IPC = indwelling pleural catheter; LFT = liver function tests; OTC = over-the-counter; PIS = patient information sheet; SNCIPC = Silver Nitrate-Coated Indwelling Pleural Catheter; PA = poster-anterior; VAS = visual analog scale

- a. Review of existing CXR and laboratory data will be performed during pre-screening I/E criteria review.
- b. The Baseline Assessment must take place by the end of the 14th day after consent is obtained, and ≤ 72 hours prior to placement of IPC.
- c. Follow-up on Days 7, 45, and 75 will be by telephone.
- d. Subjects must call the site to make an appointment for an unscheduled visit to assess for pleurodesis and potential IPC removal once they measure an output of ≤ 50 mL of pleural fluid on 3 consecutive drainages over a minimum of 5 days. IPC removal may or may not occur on the same day as the follow-up visit to confirm pleurodesis.
- e. An unscheduled CXR and CT scan may be performed on subjects who present with signs and symptoms consistent with potential recurrence as described in the protocol.
- f. Including current oncological treatment and analgesia requirements.
- g. A complete physical examination including vital signs (blood pressure, temperature and heart rate), blood oxygen saturations and respiratory rate.
- h. For subjects who have a screening and baseline visit on the same day, only the serum (S) pregnancy test will be required. For subjects who have screening and baseline visits on different days, both pregnancy tests will need to be conducted as indicated.
- i. For subjects with a self-reported silver hypersensitivity and who wish to be considered for enrollment in this study, a patch test will be performed to confirm silver nitrate hypersensitivity.
- j. Subjects require a baseline CXR only if they have not had one in the previous 5 days. CXR to include 3 views (single decubitus, PA and lateral) for insertion day (post-placement) and pleurodesis assessment and two views (PA and lateral) for baseline and all other follow-up visits.
- k. Clinical blood tests to include CBC, CRP, coagulation tests, urea and electrolytes and LFTs.
- l. For patients who receive SNCIPC, clinical blood tests will include serum silver testing.
- m. Pleural drainage is to take place daily until the day 14 follow up visit, and no less than 3 times per week between the day 14 follow up visit and the day 30 follow up visit.
The frequency of drainage from the day 30 visit onwards is according to clinical need. All drainages are to occur in the subject's home or in a suitable clinical area.
- n. For subjects with SNCIPC, pleural fluid samples will be collected for silver testing until the point of catheter removal.
- o. Information regarding but not limited to length of procedure for IPC insertion; hospital stay (hours); length of time IPC in place; drainage schedule/ frequency; frequency/dose/type of prescription/OTC medications; frequency/use of oxygen should be recorded in the notes and appropriate eCRF.
- p. The following should be documented in the appropriate page of the diary: all drainages, chest pain measurements (VAS), dyspnea scores (Modified Borg dyspnea scale), self-measured temperature as well as the frequency and use of oxygen, OTC and prescription medications, and unplanned hospital or emergency department visits. Chest pain, dyspnea and temperature measurements should take place after day's drainage, if appropriate.
- q. QoL measurements include chest pain and dyspnea scores (baseline assessment and insertion day [post placement and drainage] will be on the appropriate eCRF; all other time points will be captured in the subject diary) and EQ-5D-5L health status questionnaire (on the appropriate eCRF).
- r. Significant trapped lung is deemed present if any 1 of the following criteria is met: (1) CXR shows hydropneumothorax, (2) CXR shows $\geq 20\%$ of the affected hemithorax to be free of the expected lung parenchymal markings and there is no suggestion of pleural fluid, or (3) CXR shows $\geq 20\%$ of the affected hemithorax to be occupied with pleural fluid AFTER a pleural aspiration which resulted in symptoms suggestive of trapped lung.
- s. Upon removal, SNCIPC should be shipped to the designated central analytical lab for residual silver testing.

5.2 Time Point Algorithms

5.2.1. Relative Day

The date of catheter insertion will be considered relative day 0, and the day before catheter insertion will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

Date of Assessment – Date of Catheter Insertion.

5.2.2. Windows

For the purpose of statistical analysis, analysis visits will be derived in terms of relative study days since the device was implanted, based on the following table:

Table 2: Analysis Windows from Screening prior to Implant through Explant

Time Point	Scheduled Study Day	Visit Window for Analysis (Days)
Baseline	NA	< =0
Catheter Insertion	0	0
Follow-up Phone Call	7	1 - 9
Follow-up Visit	14	10 - 16
Follow-up Visit	30	17 - 32
Follow-up Phone Call	45	33 - 48
Follow-up Visit	60	49 - 63
Follow-up Phone Call	75	64 - 78
Follow-up Visit	90	79 - 93

5.3 Baseline Assessments

The study baseline assessments must take place by the end of the 14th day after study consent is obtained, and within 72 hours prior to placement of the IPC (Day -3 to Day 0). The assessment may be performed by any appropriately trained member of the study team, and should include:

- Review of inclusion/exclusion criteria
- Complete physical examination including vital signs (blood pressure and heart rate), transcutaneous blood oxygen saturations and respiratory rate
- Complete medical history with a specific focus on dyspnea symptoms, previous procedures and cancer treatments

- Review of the use of previous/concomitant treatments or medications or any other clinical condition(s)
- Gender, age, race, body weight and body height
- CXR (posterior-anterior view and lateral view), unless performed within the previous 5 days
- Urine Pregnancy Test (for subjects who have a screening and baseline visit on the same day, only the serum pregnancy test will be required.)
- Collection of blood samples
- QoL by subjective VAS score for chest pain, Modified Borg dyspnea scale, and EQ-5D-5L health status questionnaire

Subjects should have their IPC inserted within 72 hours of the baseline assessment taking place. If insertion is not possible within 72 hours, the subject will not be eligible for randomization. In this circumstance, should the subject become eligible for study entry at a later date they may be re-consented using a new unique identifier.

5.4 Efficacy Variables

5.4.1. Primary Efficacy Variable

The primary efficacy endpoint is defined as the proportion (%) of patients achieving confirmed pleurodesis without recurrence at 30 days, where pleurodesis is defined as:

- The collection of at least three consecutive drainages of ≤ 50 mL of pleural fluid over a minimum of 5 days (which begin with the first drainage of ≤ 50 mL)

And

- CXR (minimally PA, lateral, and single decubitus views), which shows opacification due to pleural fluid occupying less than one quarter of the hemithorax (as judged by the investigative study center and the blinded third party central radiology service).

The date of pleurodesis achievement is defined as the date on which the first of 3 consecutive drainages of ≤ 50 mL was recorded.

The proportion of patients achieving pleurodesis without recurrence by 30 days will be defined as the total number of patients in the Intent-to-Treat Population achieving pleurodesis without recurrence by 30 days divided by the total number of patients in the Intent-to-Treat Population. Patients who discontinue the study prior to 30 days will be counted as not achieving pleurodesis. Radiologic endpoint data will be based on scans (CXR and CT) submitted to the third party imaging core laboratory for assessment at the 30-day timepoint. Within the imaging core laboratory, a single reader will analyze the images, with 20% of those cases being over-read by another central reader, and if there is disagreement by more than 20% then a second reader will

read all of images. Clinical endpoint data will be based on data collected from the clinical study centers. The primary efficacy endpoint will be based on a combination of radiologic and clinical data. If there is disagreement, the central read will be used for the primary analyses.

5.4.2. Secondary Efficacy Variables

The following secondary endpoints will be compared between the two groups:

- Time to confirmed pleurodesis

Time to confirmed pleurodesis is defined as the duration between the study device insertion and the date a subject achieves pleurodesis.

- Time to recurrence

Time to recurrence is calculated for subjects who achieved confirmed pleurodesis. It is defined as the duration between successful pleurodesis (the first of a minimum of 3 consecutive drainages of ≤ 50 mL of pleural fluid over a minimum of 5 days) and the date the subject presents with symptoms of recurrence that is later confirmed by CXR and CT scan.

5.4.3. Exploratory Efficacy Variables

The following exploratory analysis will be performed comparing the two treatment groups:

- Proportion of surviving subjects without trapped lung diagnosis following IPC placement who have confirmed pleurodesis without recurrence at 14, 30, 60, and 90 days
- Proportion of subjects with confirmed pleurodesis without recurrence by 30 days after IPC placement by cancer type (lung, breast, and others)

5.5 Safety Assessments

5.5.1 Duration of Exposure

Duration of exposure is defined as the number of days since the catheter was installed. Descriptive statistics for serum and pleural fluid silver levels by time point will be provided for subjects who receive SNCIPC.

5.5.2 Incidence of IPC Occlusion

Incidence of IPC occlusion is defined as the proportion of subjects who experience IPC occlusion while on the study.

5.5.3 Incidence of Empyema and Cellulitis

Incidence of empyema and cellulitis is defined as the proportion of subjects who experience empyema or cellulitis, as coded by MedDRA and described in the data management plan, while on the study.

5.5.4 Silver Testing

Serum and pleural fluid silver levels will be measured at regular intervals for the SNCIPC subjects using the gold-standard inductively coupled plasma mass spectrometry (ICP-MS) analysis. At the time of SNCIPC removal, the SNCIPC will be inspected for structural integrity and shipped to the designated analytical laboratory for residual silver testing.

5.5.5 Adverse Events

AEs that occur during the study after the subject has signed the informed consent form (ICF) are to be collected and reported on the eCRF, regardless of whether they are reported by the subject, elicited by Investigator questioning, detected through physical examination, or by other means.

As far as possible, each AE is described by:

- duration (start and end dates)
- start/end of study medication
- severity grade (mild, moderate, severe)
- Investigator causality (relationship to the study product)
- action(s) taken (concomitant medication, change of study medication etc.) including start and end of respective action

- concomitant diseases and respective medication in general
- start, end and dosage of rescue medication
- outcome

Partial dates for adverse events captured at a study visit with day or day and month missing will be imputed as follows:

- The missing day of onset of an adverse event will conservatively be set to the earlier of:
 - First day of the month that the AE occurred, as long as the first date of the month is after the date of implantation or if the month of the onset of AE is before the date of implantation,
 - One day after implantation, if the month of the onset of AE is the same month as the month of implantation
- The missing day of resolution of an adverse event will be set to the last day of the month of occurrence.
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
 - January 1 of the year of onset, as long as this date is after implantation,
 - One day after implantation, if this is the same year that the AE occurred.

If the resolution date of an adverse event is missing both day and month, it will be set to December 31 of the year.

AE

An AE is any untoward medical occurrence (change in anatomical, physiological, or metabolic function) in a subject, which does not necessarily have any causal relationship with the product under investigation. In the event of an AE, the subject will be followed until the resolution of the AE.

TEAE

Treatment-emergent AEs (TEAEs) are those AEs whose onset occurs any time on or after the date of device insertion, up to 30 days after the last visit.

Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

ADE

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use (IFU), deployment, implantation, installation, or operation, or any malfunction of the

investigational medical device. The definition also includes any event resulting from use error or from intentional misuse of the investigational medical device. Further details regarding anticipated ADEs are provided in Section 4.2 of the study protocol.

UADE

An unanticipated ADE (UADE) is any serious AE on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

SAE

A serious adverse event (SAE) is defined in the ISO 14155 standard as an AE that led to death or to a serious deterioration in the health of the subject that either resulted in:

- a life threatening illness or injury, or,
- a permanent impairment of a body structure or a body function, or,
- in-patient or prolonged hospitalization, or,
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

An Unanticipated Serious Adverse Device Effect (USADE) is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: 'Anticipated' means an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Events that require intervention to prevent one or more of the outcomes listed in the definition above are also to be considered as serious. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalization, or development of drug dependency or drug abuse.

However, medical judgment will be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not-serious is made independently of any attribution of causality.

Events NOT considered to be SAEs are those that require:

- treatment, which is elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and does not worsen
- treatment on an emergency, out-patient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission. For the purpose of this study, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay).

AE Intensity

AE intensity determined by the clinical Investigator on the basis of his/her direct observations or the subject's reporting:

- Mild: causes no limitation of usual activities; the subject may experience slight discomfort
- Moderate: causes some limitation of usual activities; the subject may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

AE Causality (relationship guide)

Any AE has to be judged for causality (relationship to study device and relationship to study procedure).

The relationship of an AE to the study product is to be graded on the basis of the following:

- Probable: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected product; that is confirmed by an improvement on stopping the product; and that cannot be reasonably explained by the subject's clinical state
- Possible: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected device; but that may have been produced by the subject's clinical state or other therapeutic interventions on him/her
- Unlikely: a reaction that occurs with an improbable temporal sequence from administration of the product; that can be explained by the clinical state of the subject/participant or by other therapeutic interventions or other drugs or underlying disease providing plausible explanations
- Unrelated: a reaction that occurs without a reasonable temporal sequence from administration of the product; that can be explained by the clinical state of the subject or by other therapeutic interventions on him/her and that does not improve or disappear following interruption of the product

Handling of AEs

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the study product has to be discontinued if appropriate. Follow-up evaluations of the subject are to be performed until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant.

If clinically significant laboratory abnormalities appear at the final visit, appropriate additional tests may to be performed to clarify the nature of any clinically significant laboratory abnormalities that occur.

AEs are monitored and registered on the AE form of the eCRF at each visit. In absence of a specific diagnosis, an individual AE form has to be filled in for each sign or symptom.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of monitoring of persistent AEs will be provided in the monitoring plan. If an AE is still not resolved at the end of the study, this will be documented as ongoing.

For recurrent AEs, i.e., AEs of the same nature, but with a different date of onset, an individual AE form has to be completed for each of them.

AEs occurring after the termination of the study individually and/or of the study in total are to be reported to CareFusion even after the clinical study has been finished if, in the judgment of the Investigator, there is an association between the event and the previous use of the product under investigation.

If the AE is classified as serious, the clinical Investigator has also to complete the SAE report form. It is the responsibility of the Investigator to send the SAE report form by fax or email to the Global Safety Department of Chiltern International Inc. within 1 working day and to retain the original copy of the form (keeping a photocopy in the Investigator Site File). At the earliest possible date, the SAE report form must be followed by a detailed report and any documentation that may be available, e.g., hospital case records, autopsy reports, and/or other pertinent documents.

If the AE is classified as UADE, the clinical Investigator must report the UADE to Chiltern within 1 working day.

The Investigator will be responsible for reporting the SAE to ethics committees. Chiltern International Inc. will be responsible for initial reporting of SAEs/UADEs to the sponsor with narratives and follow-up reports. The safety team will also be responsible for reporting expedited safety reports to international sites and regulatory authorities and Central Ethics Committees, distributing periodic line listings to international sites and regulatory authorities and Central Ethics Committees as required per local regulation.

Pregnancy

While not considered an SAE unless a serious criterion is met, pregnancies occurring in subjects enrolled in the study or in their partners must be reported and followed to outcome. The Investigator should complete the pregnancy report form and submit within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the follow-up pregnancy report form should be completed and submitted via fax to the Global Safety Department of Chiltern International Inc. Spontaneous abortions should always be reported as SAEs.

The safety officer will forward pregnancy reports to CareFusion the next business day. Pregnancies occurring up to 30 days after the last follow-up should be reported. In the event the pregnancy outcome occurs following EOS, the Investigator will report the pregnancy outcome directly to CareFusion.

5.5.6 Clinical Laboratory Evaluations

Clinical laboratory tests are scheduled at the pre-screening visit, the baseline assessment prior to SNCIPC insertion, and at each post discharge clinical visit. The baseline value will be the latest result obtained prior to the insertion of study device. Change from baseline to each visit will be defined as the visit value minus the baseline value. All clinical laboratory test results will be reported in or converted to Standard SI units for analysis. Clinical laboratory results will also be classified as either high (H) or low (L), if the value is outside the normal reference range for the specified parameter.

5.5.7 Other Observations Related to Safety

5.5.7.1 Vital Signs

Vital signs collected will include the following: blood pressure, heart rate, respiratory rate and temperature. The Baseline value will be the latest result obtained within 72 hours prior to the insertion of study device.

5.5.7.2 Physical Examination

Physical Examination findings will be determined by the investigator as normal or abnormal.

5.5.8 Quality of Life and Medical Resource Utilization Assessments

The following quality of life and medical resource utilization endpoints will be compared between the 2 treatment groups:

- Pain using 100 mm VAS scale
- Dyspnea relief (breathlessness) using Modified Borg dyspnea scale
- Health status as measured by the EQ-5D-5L health status questionnaire
- MRU data
 - length of procedure;
 - hospital stay [hours], unplanned in-hospital medical procedures as a result of IPC placement;
 - emergency department visits related to IPC placement;
 - length of time IPC in place;
 - drainage schedule and frequency;

- frequency, dose, and type [brand name/generic] of prescription and OTC medications;
- frequency and use of oxygen;
- services required to diagnose, treat, and follow up AEs

6. STATISTICAL METHODS

6.1 General Methodology

All statistical tests will be one-sided with a significance level of $\alpha=0.025$, unless specified otherwise, and will be performed using SAS® Version 9.2 or higher. Data will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables. When appropriate, two sided 95% confidence intervals may be used.

Subject listings of all data from the case report forms (CRFs) as well as any derived variables will be presented.

6.2 Adjustments for Covariates

The primary analysis does not have any adjustments for covariates.

6.3 Handling of Dropouts or Missing Data

For the primary efficacy analysis, if a patient discontinues the study prior to 30 days, the subject will be counted as not achieving pleurodesis (considered a “failure”). Missing data will not be imputed.

In all other efficacy analyses, subjects who discontinue from the study will be considered a “failure”. For time to event variables, subjects who discontinue the study will be censored at the time of discontinuation. Subjects who do not experience the event and did not discontinue the study will be censored at the subject’s last visit.

6.4 Interim Analyses and Data Monitoring

Stopping rules will be defined by the DSMB and outlined in the DSMB charter, as described in Section 1.9 of the study protocol. The stopping rules are based on safety criteria. There will be no consideration for stopping based on efficacy.

There will be an unblinded sample size evaluation at interim. Sample size adjustment will be based on the promising zone approach as detailed in Mehta and Pocock³¹. Unblinding will be performed by individuals with unblinding access as described in section 4.4.

The interim analysis will be conducted once 2/3 of the information is available, when 80 subjects are evaluable for the primary endpoint under the superiority hypothesis with the purpose of determining whether the sample size should be increased to ensure sufficient power at the final analysis. The study will not be stopped prematurely for efficacy prior to the 119 subjects being enrolled. Through simulation based on the methods outlined in Wang et al³², it was determined that the Type I error is controlled under 0.025 (Appendix 4 of the SAP). The below rules will be followed.

The decision rules for this design adaptation will be as follows:

Unfavorable Zone: $CP < 0.395$ → Study size will remain the same at 119

Promising Zone: $0.395 \leq CP < 0.8$ → Study size will be increased to 179

Favorable Zone: $CP \geq 0.8$ → Study size will remain the same at 119

where CP is the conditional power at interim and 0.395 is the minimum CP derived from conservative extrapolation from Table 1 in Mehta and Pocock³¹ to determine the unfavorable zone.

6.5 Multi-center Studies and Pooling of Centers

No single site will enroll more than 40 subjects without prior approval from the Sponsor. In the event that there are small sample sizes at some sites, sites may be grouped using the following procedure to create “analysis-sites” for analysis purposes. These analysis-sites will be created for US and UK independently to preserve the ability to differentiate between countries. Analysis-sites are based on a target size of at least 5 subjects per treatment group at each site. If investigative sites have at least 5 ITT subjects per treatment group, they will retain their identities in the analyses. All Investigative sites with fewer than 5 ITT subjects per treatment group will be rank ordered by size and sorted secondarily by site identification number to break ties. Starting with the smallest investigative site, subjects will be combined site by site by treatment group, until the first time the resulting analysis-site has at least 5 ITT subjects in each treatment group. The process continues until all investigative sites are accounted for. If the last analysis-site has fewer than 5 ITT subjects per treatment group, it will be combined with the most recently created analysis-site.

Although a site effect is not anticipated, the homogeneity of treatment effect across analysis-sites will be tested using a Breslow-Day test at a two-sided 15% alpha level. If the Breslow-Day test is significant at 15% level, a meta-analysis will be performed to investigate treatment differences across analysis-sites.

The proportion (and 95% CIs) of patients achieving pleurodesis without recurrence at 30 days will be presented for each treatment group by analysis-site for descriptive purposes.

6.6 Multiple Comparisons/Multiplicity

Serial gatekeeping procedures (Dmitrienki and Tamhane²⁹) will be used to preserve the overall alpha of the study at the one-sided 2.5% level. The endpoints will be tested sequentially in the following order with no adjustments for multiplicity:

- 1) Superiority test on the primary endpoint
- 2) Non-inferiority on the first secondary endpoint (time to pleurodesis)
- 3) Superiority on the first secondary endpoint (time to pleurodesis)
- 4) Non-inferiority test on the second secondary endpoint (time to recurrence)
- 5) Superiority on second secondary endpoint (time to recurrence)

Each of above endpoints will be tested for superiority using a one-sided alpha of 2.5%.

Exploratory, safety, QOL and MRU analyses will not be considered for alpha spending since they will be evaluated for investigative purposes only. Any results obtained from these analyses will not be considered as a basis for any claims.

6.7 Use of an “Efficacy Subset” of Subjects

In addition to analyzing the primary endpoint on the Intent-to-Treat Population, a sensitivity analysis will be conducted in the exact same manner using the Per-Protocol Population to ascertain that the results are robust.

6.8 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

6.9 Examination of Subgroups

If at least 80% of the total number of US subjects participating in this study are Medicare beneficiaries, then no subgroup analysis will be conducted. However, if less than 80% of all US subjects enrolled are Medicare beneficiaries, then a subgroup analysis will be conducted to evaluate outcomes specifically for the Medicare beneficiaries enrolled in the study. All primary and secondary outcomes for the subgroup analyses will be the same as for the main analysis. For this analysis, the Medicare population will be defined as any subject recruited in the US, who is:

- at least 65 years old (even if he/she did not indicate Medicare as primary insurance),
- or under 65 years old, and receives Medicare health insurance (due to a disability).

7. STATISTICAL ANALYSIS

7.1 Disposition of Subjects

The number of patients randomized, who had the study device inserted, and are in the ITT population will be summarized. The number of treated patients who completed the study, the number of patients who discontinued from the study and the reasons for discontinuing from the study will also be summarized.

7.2 Protocol Deviations

Protocol Deviations will be evaluated as per the clinical database and additionally as tracked by operational study team members. The information available from both sources will be evaluated at Blinded Data Review Meetings (BDRM) prior to close of the database. The specific data displays will be agreed on in a separate BDRM checklist document. The decision about major protocol violations and assignments to populations will be documented in the BDRM meeting minutes.

7.3 Analysis Populations

7.3.1. All Randomized Population

All subjects randomized to either the study device or the control device will be included in the All Randomized Population. Subjects in the All Randomized Population will be analyzed according to their randomized treatment group.

7.3.2. Safety Population

Subjects in the All Randomized Population who received either the study device or the control device will be included in the Safety Population. Subjects in the Safety Population will be analyzed according to the treatment group received.

7.3.3. Intent-to-Treat (ITT) Population

All subjects randomized to either the study device or the control device and received one of the treatments will be included in the Intent-to-Treat Population. Subjects in the Intent-to-Treat Population will be analyzed according to their randomized treatment group.

7.3.4. Per Protocol (PP) Population

Subjects in the ITT Population who do not have major protocol deviations will be included in the Per Protocol (PP) Population. The major protocol deviations will be defined at the time of evaluability evaluation to occur in a blinded manner and finalized before database lock and unmasking.

7.4 Demographic and Other Baseline Characteristics

All baseline summaries will be based on the All Randomized and ITT populations.

Gender and race will be summarized using counts and percentages. Age, height (cm), and weight (kg) will be summarized with descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]). Age may be summarized by decades using N and %. Other baseline characteristics may be summarized as necessary.

Similar summary statistics for background and demographic characteristics for only the ITT population will also be done by center. No inferential statistics will be made on these characteristics.

7.5 Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary version September 2014 will be used to classify medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

Medications will be summarized using counts and percentages by WHO ATC classification of ingredients and by preferred term. Anticoagulants will be summarized separately. This summary will be performed for ITT population.

Medications with start date and stop date prior to insertion of study device will be included in the prior medication summary. Medications taken during the study, including those started prior to insertion of study device, will be included in the concomitant medication summary.

Partial dates for concurrent medications captured at a study visit with day or day and month missing will be imputed as follows:

- The missing day of start date of a concurrent medication will conservatively be set to the earlier of:
 - First day of the month that the concurrent medication was taken, as long as the first date of the month is after the date of implantation or if the month of the start of concurrent therapy is before the date of implantation,
 - One day after implantation, if the month of the start of concurrent medication is the same month as the month of implantation.
- The missing day of end date of a concurrent medication will be set to the last day of the month the concurrent medication was taken.
- If the start date of a concurrent medication is missing both day and month, it will be set to the earliest of:
 - January 1 of the year of start of medication as long as this date is after implantation,
 - One day after implantation, if this is the same year that the concurrent medication was taken.

If the end date of a concurrent medication is missing both day and month, it will be set to December 31 of the year.

7.6 Analysis of Efficacy Parameters

7.6.1. Analysis of Primary Efficacy Variables

The primary objective is to demonstrate that the SNCIPC Pleural Catheter shows superiority compared to the PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence at 30 days.

$$H_0: pT - pC \leq 0 \quad \text{versus} \quad H_a: pT - pC > 0$$

where pT is the rate of pleurodesis without recurrence at 30 days for the study device, pC is the rate for the control device.

Rejecting the null hypothesis will establish superiority of the study device over the control device.

The primary analysis will be performed on the Intent-to-Treat (ITT) Population. A sensitivity analysis will be done using the Per-protocol (PP) Population.

7.6.1.1. Site Pooling Analysis

The effect of sites based on pooled analysis-sites as per Section 6.5 will be assessed.

7.6.2. Analysis of Secondary Efficacy Variables

For secondary objectives, 30% was selected as a clinically relevant non-inferiority margin. See appendix 2 for justification.

Time to confirmed pleurodesis analysis will be performed using a proportional hazards model and Kaplan-Meier time-to-event analysis. The analysis will be performed on all subjects in the ITT population, and on all subjects in the PP population as a supportive analysis. A proportional hazards model will be used to estimate the hazard ratio. Non-inferiority will be established if $HR > 0.7$.

Time to confirmed pleurodesis will be summarized by 25th percentile, median, and 75th percentile, when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group will be provided. Time to confirmed pleurodesis is defined as the duration between the study device insertion and the date of confirmed pleurodesis. For subjects who do not have confirmed pleurodesis, censoring rules are described in section 6.3.

Incidence density for time to confirmed pleurodesis will be evaluated between the 2 groups by summarizing the number of subjects in the ITT population, number of confirmed pleurodesis, number of subjects censored in the time to pleurodesis, and patient-days in each treatment group. Patient-days within the treatment group will be calculated as the total number of days from study device insertion to confirmed pleurodesis or termination of study participation summed for all subjects within the treatment group.

Time to recurrence analysis will be performed using proportional hazards model and Kaplan-Meier time-to-event analysis. The analysis will be performed on all subjects in the ITT population who had confirmed pleurodesis, and on all subjects in the PP population who had confirmed pleurodesis as a supportive analysis. A proportional hazards model will be used to estimate the hazard ratio. Non-inferiority is established when $HR < 1.3$.

Time to recurrence will be summarized by 25th percentile, median, and 75th percentile, when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group will be provided. Time to recurrence is defined as the duration between confirmed pleurodesis and the date of recurrence. For subjects who do not have a recurrence after confirmed pleurodesis, censoring rules and incidence density analysis will be described in section 6.3.

Incidence density for time to recurrence will be evaluated between the 2 groups by summarizing the number of subjects with confirmed pleurodesis, number of recurrences, number of subjects censored in the time to recurrence, and patient-days in each treatment group. Patient-days within the treatment group will be calculated as the total number of days from confirmed pleurodesis to recurrence or termination of study participation summed for all subjects within the treatment group.

Superiority will be demonstrated when the one-sided p-value is less than 0.025 using a proportional hazards model.

7.7 Analysis of Exploratory Efficacy Variables

Exploratory analyses include the following endpoints:

- Proportion of surviving subjects without a trapped lung diagnosis following IPC placement and who have confirmed pleurodesis without recurrence at 14, 30, 60, and 90 days

This endpoint will be analyzed in the same fashion as the primary endpoint using the surviving subjects without a trapped lung diagnosis who have confirmed pleurodesis without recurrence.

- Proportion of subjects achieving pleurodesis without recurrence by 30 days by cancer type

The proportion (%) of subjects achieving pleurodesis without recurrence by 30 days will be summarized for each treatment group by cancer type (lung, breast and others). The proportions will be compared using a Cochran-Mantel-Haenszel test using the cancer type as a stratification factor. If a subject discontinues the study prior to 30 days, he will be counted as not achieving pleurodesis (failure).

Exploratory analyses will be performed on the ITT Population and repeated on the PP population as supportive analyses.

7.8 Analysis of Safety

All safety analyses will be performed on the Safety Population. All comparisons between treatment groups for the safety parameters will be descriptive in nature.

7.8.1. Duration of Exposure and Compliance

The duration of subject exposure will be quantified as the number of days between IPC insertion and removal. It will be listed and summarized for all subjects in the Safety Population by treatment group. Compliance will not be calculated.

7.8.2. Incidence of Catheter Occlusion

Incidence rate of IPC occlusion is defined as proportion of subjects who experienced IPC occlusion while on study. It will be summarized for all subjects in the Safety Population by treatment group. Fisher's exact test will be used to compare between treatment groups.

7.8.3. Incidence of Empyema and Cellulitis

Incidence rate of empyema and cellulitis while on study, as coded by MedDRA and described in the data management plan, will be summarized for all subjects in the Safety Population by treatment group. Fisher's exact test will be used to compare between treatment groups.

7.8.4. Serum and Pleural Fluid Silver Levels

Serum and pleural fluid silver levels will be measured at regular intervals for the SNCIPC subjects using the gold-standard inductively coupled plasma mass spectrometry (ICP-MS) analysis. It will be summarized for all subjects who received SNCIPC by summary statistics (N, mean, median, standard deviation, minimum and maximum values). At the time of SNCIPC removal, the SNCIPC will be shipped to the designated analytical laboratory for residual silver testing. This data will be summarized for all subjects who received SNCIPC by summary statistics.

7.8.5. Adverse Events

The Investigator's verbatim term of each AE will be mapped to system organ class and preferred term using MedDRA dictionary version 17.1 or higher.

AEs will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment. Subject counts and percentages and event counts will be presented for each treatment group and totaled for all treatment groups for the following:

- All TEAEs
- All AEs by severity
- All SAEs
- All ADEs
- All SADEs
- All UADEs and USADEs

Comparison between two treatment groups for frequency of any AEs, and frequency of any ADEs will be done using a Fisher exact test.

Listings will be presented by subject for all AEs as well as SAEs, deaths, and AEs leading to discontinuation from the study.

7.8.6. Clinical Laboratory Evaluations

Clinical laboratory results at each time point and for change from baseline will be displayed using summary statistics (N, mean, median, standard deviation, minimum and maximum values).

All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L). In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to specified time point. Baseline is defined as the latest result obtained prior to the insertion of study device.

7.8.7. Other Observations Related to Safety

7.8.7.1. Vital Signs

Pre-implantation values, post-implantation values, and the change from baseline in vital sign measurements (BP, HR, RR, and TEMP) will be summarized with descriptive statistics (n, mean, SD, median, min, and max) at each time point by treatment. The baseline value will be the latest value obtained within 72 hours prior to the insertion of the study device.

All vital signs will be listed.

7.8.7.2. Physical Findings

The number and percentage of subjects with abnormal findings on physical examination will be summarized by organ system.

All physical examination findings will be listed.

7.8.8. Quality of Life and Medical Resource Utilization Parameters

7.8.8.1. Quality of Life and Medical Resource Utilization Parameters

7.8.8.1.1. 100 mm VAS for Pain

For each treatment group, VAS data collected at baseline and at each subsequent time point will be summarized using descriptive statistics. At each time point, comparison between the two treatment groups will be done using a two-sample t-test. Change from baseline between the two treatment groups will be analyzed using a two-sample t-test.

7.8.8.1.2 Modified Borg Dyspnea Scale

The Borg scale measures the intensity of dyspnea on a scale from 0-10. Higher numbers indicate greater difficulty with breathing. Based on previous research, a 1-point change in the Modified Borg scale will be considered a minimally clinically important difference. For each treatment group, Borg scale data collected at baseline and at each subsequent time point will be summarized using descriptive statistics. At each time point, comparison between the two treatment groups will be done using a two-sample t-test. Change from baseline between the two treatment groups will be analyzed using a two-sample t-test.

7.8.8.1.3 EQ-5D-5L

The EQ-5D-5L includes two components: a questionnaire with 5 questions and a VAS.¹ For each of the five questions, there are five possible response options ranging from ‘no problem’ (Level 1) to ‘extreme problem’ (Level 5). The five questions are scored separately, each categorically. Note: there should only be one response for each dimension. If a subject marked more than one response, then that dimension should be set to missing. The EQ-5D-5L data collected at baseline and at each subsequent time point will be summarized using descriptive statistics (number and percentage of subjects for each potential item response). The comparison between treatment groups and change from baseline will be done with the categorical data using the chi-square test, or Fisher’s exact test if more appropriate.

7.8.8.1.4 EQ-5D-5L-VAS

The EQ-5D-5L also includes a VAS from 0-100 that asks the respondent to indicate how his/her health is today by marking an “X” on the line and writing the corresponding number in a box. If the number in the box does not match the X in the VAS, then the number in the box should be used for analysis purposes. For each treatment group, VAS data collected at baseline and at each subsequent time point will be summarized using descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, minimum, and maximum). At each time point, comparison between the two treatment groups will be done using a two-sample t-test. Change from baseline between the two treatment groups will be analyzed using a two-sample t-test.

All quality of life assessment results will be listed.

7.8.8.2. Medical Resource Utilization Parameters

Comparison between the 2 treatment groups involving continuous variables such as length of procedure, length of hospital stay and length of time IPC in place will be done using a t-test. All categorical resource utilization data including medication use, outpatient visits and other treatments will be summarized using descriptive statistics and compared using Fisher’s exact test. Missing values will not be imputed for these measures.

All medical resource utilization data will be listed.

8. COMPUTER SOFTWARE

All analyses will be performed by Chiltern International Inc. using Version 9.2 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

For continuous variables, descriptive statistics (number of subjects [N], mean, standard deviation [SD], median, minimum, and maximum) will be generated. For discrete/categorical variables, the number and proportion of subjects will be generated. The standard operating procedures (SOPs) of Chiltern International Inc. will be followed in the creation and quality control of all data displays and analyses.

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10. APPENDICES**10.1 APPENDIX 1: VARIABLE DEFINITIONS**

Age will be calculated as the informed consent date minus the date of birth divided by 365.25 [Age=(ICF Date-DOB)/365.25]. Body mass index (BMI; kg/m²) is calculated as: weight (kg) / [height (m)]², rounded to one decimal place. Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm), and temperature will be displayed in Celsius (C). Weights, heights, or temperatures recorded in alternate units will be converted to the units being displayed using standard conversion formulas.

10.2 APPENDIX 2: Meta-Analysis

The primary analysis in previous protocol versions was a non-inferiority hypothesis for the rate of pleurodesis. A non-inferiority margin of 6.6% (or 30% of the 22% estimated PleurX rate) was established based on the analysis presented below. The 30% clinically relevant margin will continue to be used as a non-inferiority margin for hazard ratios for secondary objectives.

Van Meter et al³⁴ aggregated published data using a rigorous search strategy on tunneled indwelling pleural catheter (TIPC) encompassing 19 studies with 1,370 patients. Thirteen of these reported rates of spontaneous pleurodesis and are included in our meta-analysis below.

Study		Patients (N)	Spontaneous Pleurodesis Events/Evaluable*	Percent
1	Putnam et al, 1999	99	42/91	46.2
2	Putnam et al, 2000	100	21/100	21.0
3	Pollak, 2001	28	13/31	41.9
4	Ohm, 2003	34	4/34	11.8
5	Wyckoff, 2003	18	7/18	38.9
6	Musani, 2004	24	11/19	57.9
7	Tremblay, 2006	223	103/240	42.9
8	Al-Halfawy, 2008	55	42/55	76.4
9	Diez-Porres, 2008	8	2/7	28.6
10	Bazerbashi, 2009	125	95/125	76.0
11	Bertolaccini, 2009	77	48/77	62.3
12	Schneider, 2009	100	29/100	29.0
13	Sioris, 2009	51	11/51	21.6
*Includes bilateral catheter placement and pleurodesis evaluation in some patients				

Results for a 30-day pleurodesis rate are not widely available. However, we are able to obtain an overall weighted estimate of the rate of spontaneous pleurodesis using the above data in order to provide an estimate of variability which then assists in defining a NI margin⁴⁶. A meta-analysis on the above proportions is performed, after converting to $\ln(\text{odds})$, employing the inverse variance weighting method and a random effects model.^{47,48}

Results of the meta-analysis give point estimate (95% CI) on the natural logarithmic scale - 0.3293 (-0.8812, 0.2225). Transforming back to the original scale gives 41.8% (29.3%, 55.5%).

From the protocol, the 30-day proportion pleurodesis success rate, with consideration for trapped lung and dropout, is estimated as 22% for the PleurX group. Considering a 30% NI margin, which is deemed clinically meaningful, the resulting NI margin is $-0.3 * 22\% = -6.6\%$. This is much smaller than the distance from the lower CI to the point estimate in the meta-analysis (12.5%).

The 30% relative margin is used for secondary objectives.

10.3 APPENDIX 3: STATISTICAL ANALYSIS AND PROGRAMMING DETAIL

Exact binomial confidence intervals on one treatment group rate:

- *Make sure the outcome variable is coded properly since BINOMIAL option computes the binomial proportion and confidence limits for the first level of the variable. For example, if outcome is coded 'pleurodesis vs. no pleurodesis' the output will have test statistics and confidence limits for pleurodesis. If the outcome is coded 'no pleurodesis vs. pleurodesis', then output will have test statistics and confidence limits for failure to achieve pleurodesis.*
- *Make sure appropriate alpha is specified since the procedure always produces 2-sided confidence limits.*
 - *To obtain 2-sided 95% confidence limits, specify alpha=0.05*

Exact binomial confidence intervals on difference in proportions of two treatment groups:

- *Make sure the outcome variable is coded properly since BINOMIAL option computes the binomial proportion and confidence limits for the first level of the variable. For example, if outcome is coded 'yes vs no' the output will have test statistics and confidence limits for not having the event. If the outcome is coded '0 vs 1', then output will have test statistics and confidence limits for whichever answer is coded as 0.*
- *Make sure the treatment variable is coded so the SNCIPC device comes first or last depending on the analysis. For primary endpoint SNCIPC device needs to come first in the frequency table since difference in proportions needs to be SNCIPC – Control.*
- *Make sure appropriate alpha is specified since the procedure always produces 2-sided confidence limits.*
 - *To obtain 2-sided 95% confidence limits, specify alpha=0.05*

The following is example syntax of SAS code to produce the 2-sided 95% exact binomial confidence intervals.

```
ODS OUTPUT RiskDiffColl=_stat(KEEP=row risk ExactLowerCL
ExactUpperCL);
PROC FREQ DATA=sur6;
    WEIGHT n;
    TABLE group*outcome / BINOMIAL ALPHA=0.05;
    EXACT RISKDIFF; /*(P1 - P2) */
Run;
```

where n is total number of patients with event and total number of patients without an event for each group. Outcome = No Event or Event depending on endpoint.

Kaplan-Meier (KM) Time to Confirmed Pleurodesis Analysis:

The SAS procedure LIFETEST will be used for Kaplan-Meier time-to-event analysis.

- *Censored = 1 for all patients not experiencing the event, patients discontinued, or lost to follow-up*

- *Censored = 0 for all patients experiencing the event*

The following code will be used:

```
ods listing close;
ods output CensoredSummary=censor quartiles=_qt;
PROC LIFETEST DATA = pleur METHOD=km ALPHA=0.05 OUTSURV=interval
    TIMELIM=n;
    TIME pleurdays*censored(1);
    STRATA trtmnt;
    ID usubjid;
run;
ods listing;
ods output close;
```

- *pleurdays= number of days until confirmed pleurodesis*
- *dataset censor contains number of patients censored for this analysis*
- *data _qt contains KM 25th percentile, median, and 75th percentile estimates of time to confirmed pleurodesis*

10.4 APPENDIX 4 Simulation

Simulation code (SAS) is below along with key results. (Reference: Wang C, Keller DS and Lan KKG. (2002) Sample Size Re-estimation for binary data via conditional power. JSM Meetings – Biopharmaceutical Section, pp 3621-3626.) :

```
%let N = 1000; * note that simulation run-time is long due to exact CIs;
%let Mt = 79;
%let nti = 53;
%let inct1 = 26;
%let inct2 = 66;
%let pt0 = 0.22; *key line to change for different scenarios;
%let Mc = 40;
%let incc1 = 13;
%let incc2 = 33;
%let nci = 27;
%let pc0 = 0.22;
%let deltasup = 0;
%let deltani=0.066;
%let cL = 0.395;
%let cU = 0.8;
title "pT=&pt0., pC=&pc0., Simulation replicates=&N";
data interim (keep = xt1 xc1 );
    call streaminit(123);
    ***Generate Stage 1 Data ***;
    do i = 1 to &N.;
        xt1 = rand("Binomial",&pt0., &nti.);
        xc1 = rand("Binomial",&pc0., &nci.);
        output;
    end;
run;

data intcalc (keep = xt1 xc1 p_hat_t_i p_hat_c_i SE Z tau B Theta CP_stat
CP);
    set interim;
    p_hat_t_i = xt1 / &nti.;
    p_hat_c_i = xc1 / &nci.;
    d = p_hat_t_i - p_hat_c_i;
    SE = sqrt((p_hat_t_i * (1-p_hat_t_i)/&nti.) + (p_hat_c_i*(1-
p_hat_c_i)/&nci.));
    Z = (p_hat_t_i - p_hat_c_i + &deltasup.) / SE;
    tau = (&nti.+&nci.)/(&Mt.+&Mc.);
    B = Z * sqrt(tau);
    Theta = B / tau;
    CP_stat = (1.96 - B/tau) / sqrt(1-tau);
    CP = 1 - probnorm(CP_stat);
run;

***Generate stage 2 data ***;
data full;
    set intcalc (keep = xt1 xc1 p_hat_t_i p_hat_c_i cp);
    if (CP < &cL.) then do;
        zone=1; inct = &inct1.; incc = &incc1.;
    end;
    if (CP >= &cL. and CP < &cU.) then do;
```



```

        zone=2; inct = &inct2.; incc = &incc2.;
    end;
    if (CP >= &cU.) then do;
        zone=3; inct = &inct1.; incc = &incc1.;
    end;

    call streaminit(432);
    xt2 = rand("Binomial",&pt0., inct);
    xt = xt1 + xt2;
    nt = &nti. + inct;
    p_hat_t = xt / nt;
    yt=nt-xt;
    xc2 = rand("Binomial",&pc0., incc);
    xc = xc1 + xc2;
    nc = &nci. + incc;
    p_hat_c = xc / nc;
    yc=nc-xc;
    replicate=_N_;
run;

proc transpose data=full out=stackedDf(rename=(coll=Count));
    var xc yc xt yt;    by replicate;
run;

data stackedDf;
set stackedDf;
if _NAME_="xc" then do;
    Trt=0;Response=1; end;
if _NAME_="yc" then do;
    Trt=0;Response=0; end;
if _NAME_="xt" then do;
    Trt=1;Response=1; end;
if _NAME_="yt" then do;
    Trt=1;Response=0; end;
run;

ods select none;
ods output RiskDiffColl=PropDiff;
PROC FREQ DATA=stackedDf;
WEIGHT count;
by replicate;
TABLE trt*response / BINOMIAL ALPHA=0.05;
EXACT RISKDIFF;
Run;

data Propdiff;
set propdiff;
where Row="Difference";
if ExactLowerCL>0 then reject_sup=1;else reject_sup=0;
if ExactLowerCL>-(&deltani.) then reject_ni=1; else reject_ni=0;
run;

ods select all;
proc freq data=full;
tables zone;

```

```
run;
proc freq data=Propdiff;
tables reject_ni reject_sup;
run;
```

The simulation results for non-inferiority Type 1 error, superiority Type 1 error, and superiority power are below (1000 replications per row). Note that non-inferiority analysis for the primary endpoint was planned for previous protocol versions and will not actually be performed under current protocol version.

					Zone distribution at interim analysis (%)		
pT ₀	pC ₀	Type I (Sup)	Type 1 (NI)	Power (Sup NI)	Cp<0.395 Zone 1	0.395≤Cp≤0.8 Zone 2	Cp>0.8 Zone 3
0.154	0.22	NA	0.005	NA	98	1.5	0.5
0.22		0.005	NA	NA	91.5	5.4	3.1
0.48		NA	NA	0.782 0.947	16.6	15.6	67.8

From the above, it is demonstrated that the adaptive trial properly controls Type 1 error under 0.025. In fact, the estimated Type 1 error based on simulations was 0.005 for both superiority and non-inferiority (note that non-inferiority analysis will not be performed per previous discussions with agency). Type 1 error is lower than 0.025 because exact confidence intervals for proportion difference are in general conservative even for fixed, non-adaptive designs.